Gut 1993; **34**: 570–572

Multisystem Langerhans' cell histiocytosis with pancreatic involvement

R C H Yu, A Attra, C M Quinn, T Krausz, A C Chu

Abstract

Langerhans' cell histiocytosis, a rare disorder of unknown cause affecting both children and adults, can affect many different organs and present to a wide range of medical specialties. An infant with fatal multisystem Langerhans' cell histiocytosis in whom the pancreas and the intestine were extensively affected is reported. The direct pancreatic involvement by this disease has not previously been described.

(*Gut* 1993; **34**: 570–572)

Unit of Dermatology, and Department of Histopathology, Royal Postgraduate Medical School, London
R C H Yu
C M Quinn
T Krausz
A C Chu

Department of Haematology/Oncology, Hospital for Sick Children, London
A Attra

Correspondence to:
Dr R Yu, Unit of Dermatology, Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road, London W12.

Accepted for publication 31 August 1992

Case report

An 8 month old boy presented with a skin rash, a discharging right ear, and easy bruising from the age of 3 months. Clinical examination showed a seborrhoeic dermatitis like rash affected the scalp and purpuric erythemato-papular lesions in the axillary flexures, perineum, and sacral regions. There was moderate hepatosplenomegaly.

Laboratory investigations showed a moderate pancytopenia. Biopsy specimen of lesional skin showed the papillary dermis contained a patchy infiltrate of large cells with cleaved nuclei and abundant, faintly eosinophilic cytoplasm. Bone marrow trephine and aspirate also showed islands of similar histiocyte like cells with typical oval indented nuclei. Immunostaining of these cells showed them to be positive for S100 protein and peanut agglutinin. A definitive diagnosis of multisystem Langerhans' cell histiocytosis was made according to the criteria of the Histiocyte Society.[1]

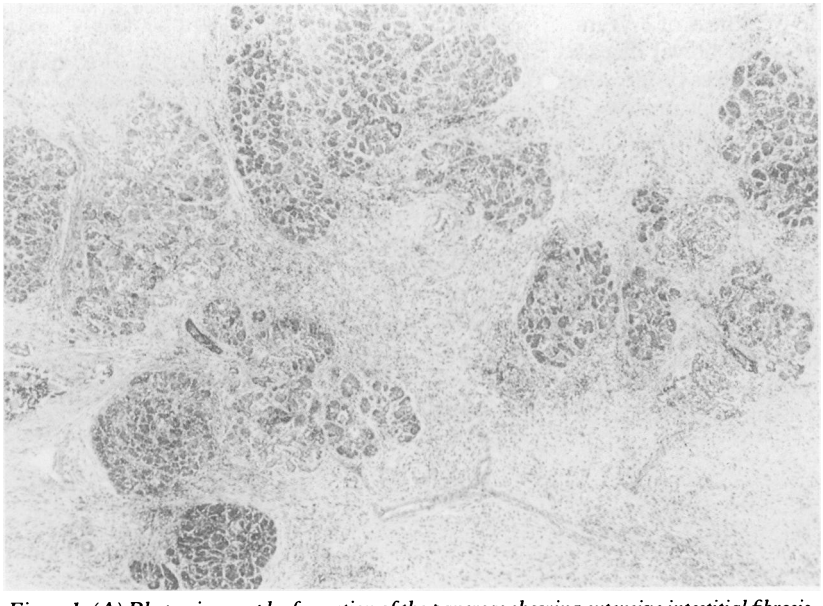

Figure 1: (A) Photomicrograph of a section of the pancreas showing extensive intestitial fibrosis with focal lobular atrophy. (Haematoxolyin and eosin, original magnification ×25.)

The child's condition deteriorated over the following 9 months with repeated episodes of febrile illness, increasing hepatosplenomegaly, and pancytopenia that necessitated frequent blood transfusions. He also suffered from severe growth retardation with his height and body weight both falling from the 75th centile at 9 months to the 30th centile at 17 months. At 13 months of age, he developed persistent unexplained abdominal pain, distension, and diarrhoea. Several systemic agents including high doses systemic steroids, etoposide (VP16), vinblastine, and cyclosporin A were administered but failed to produce complete remission. He subsequently died of bone marrow failure at the age of 18 months.

Post mortem examination findings

The main macroscopic findings were skin changes in the groins and axillae, hepatosplenomegaly, and enlargement of the head of pancreas. Histological examination of tissues confirmed the presence of histiocyte like cells with homogenous eosinophilic cytoplasm and cleaved nuclei, in the skin, lungs, bone marrow, liver, spleen, gastrointestinal tract, and pancreas. Immunocytochemical staining of the skin, bone marrow, intestine, and pancreas confirmed the presence of CD1a expressing cells in all these organs.

Pancreatic tissue showed extensive interlobular fibrosis and focal exocrine gland atrophy (Fig 1A). The fibrosis was associated with a dense infiltrate of histiocyte like cells with the characteristic features of Langerhans' cell histiocytosis cells. Other cells, including lymphocytes, plasma cells, and eosinophils, were also present. The exocrine ducts were dilated and filled with inspissated eosinophilic material. The islets of Langerhans, were however, well preserved (Fig 1B). The duodenum adjacent to the head of pancreas and the jejunum also showed extensive infiltration of the submucosa by Langerhans' cell histiocytosis cells (Fig 2A and 2B). Interestingly, the mucosa was spared, and the muscularis propria and subserosa contained only a few cells. There was no evidence of villous atrophy. The rest of the intestine was affected in a similar fashion but to a lesser degree.

Discussion

Langerhans' cell histiocytosis represents a condition characterised by an abnormal accumulation and/or proliferation of cells expressing the phenotypic markers of normal epidermal Langerhans' cells in various organs.[2,3] The clinical spectrum of this disease can be extremely variable, from asymptomatic single system

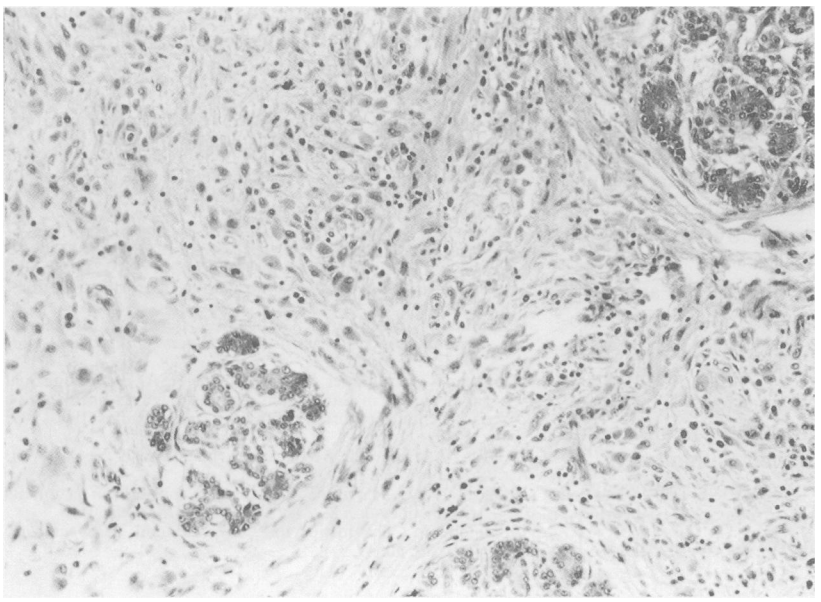

Figure 1: (B) The fibrotic areas contain numerous Langerhans' cell histiocytosis cells intermixed with lymphocytes. (Haematoxylin and eosin, original magnification ×100.)

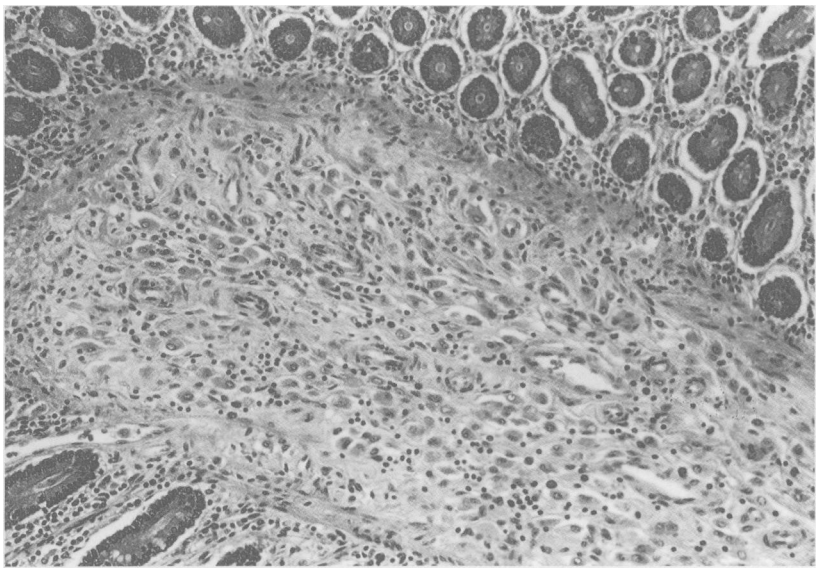

Figure 2: (A) Photomicrograph of section of jejunum showing a dense cellular infiltrate in the submucosal and mucosal layers. (Haematoxylin and eosin, original magnification ×100.)

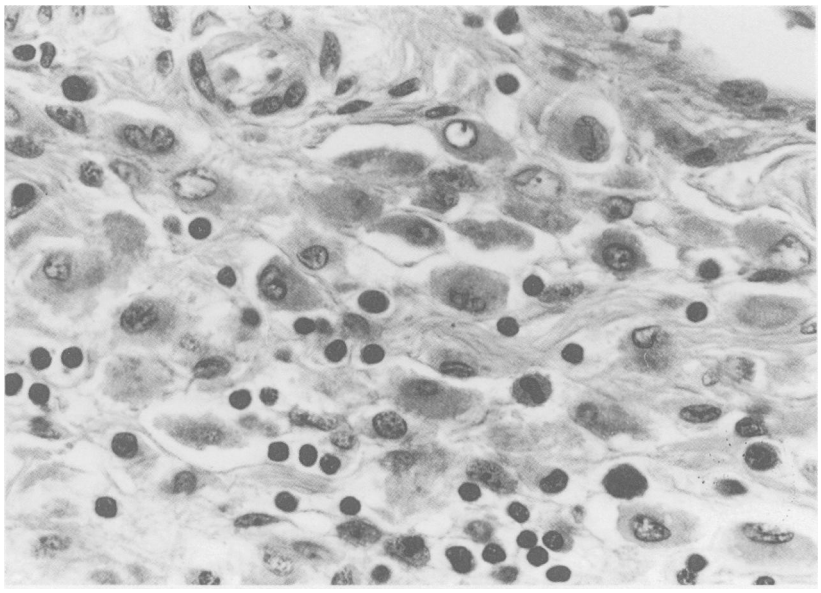

Figure 2: (B) The histiocyte like cells show characteristic histological features of Langerhans' cell histiocytosis cells.

involvement to fulminant multisystem disease, resulting in death in severe cases. The mortality tends to be highest in those children in whom it starts before the age of 2 years and the long-term sequelae are determined by the degree of organ destruction caused by the disease process.[4,5] Organs commonly affected are the skin, bone, lungs, liver, spleen, and the pituitary gland.

The gastrointestinal tract is only occasionally affected by Langerhans' cell histiocytosis, with proved gut involvement in about 1% of sufferers.[6] It is generally agreed that gut involvement is a sign of widespread disease,[7] although bowel involvement alone as the presenting sign has been reported.[8] The ileum is the most commonly affected, followed by the duodenum, jejunum, and the large bowel. Although the lamina propria is the usual site of involvement. Other parts of the wall may be affected alone or in conjunction with it.[9] The clinical presentation depends on the site and degree of bowel involvement. Diarrhoea, vomiting, abdominal pain, malabsorption, protein loosing enteropathy, and portal hypertension have all been reported.[7]

Involvement of the gastrointestinal tract, and possibly the pancreas, is likely to occur more commonly than previously recognised, and may account for some of the unexplained symptoms in some of these children. Investigations for gastrointestinal malfunction are often non-specific and technically difficult because of the young age of the patients. The Writing Group of the Histiocyte Society recommended a definitive diagnosis of Langerhans' cell histiocytosis involvement only in the presence of Birbeck granules as detected by transmission electron microscopy or the finding of CD1a determinant in the lesional cells.[1] Endoscopic biopsy at multiple sites for tissue diagnosis is the only certain way of confirming intestinal involvement. Negative specimens do not exclude the possibility of gut involvement as the lamina propria may be spared as seen in our case. The incidence of gastrointestinal involvement is likely to be grossly underestimated because of these practical difficulties in establishing the diagnosis. Many cases are confirmed only at autopsy as illustrated in our case. It should be borne in mind that the bowel may be involved in patients suffering from Langerhans' cell histiocytosis with non-specific abdominal symptoms, unexplained anaemia, or growth retardation.

Although the pancreas is an integral part of the gastrointestinal tract, direct involvement of the pancreas by Langerhans' cell histiocytosis has never been reported. Keeling *et al*[9] described the autopsy findings of 12 cases of Langerhans' cell histiocytosis with gastrointestinal involvement – the pancreas was found to be normal in all cases. The pathological changes in our case are that of a moderate infiltrate of Langerhans' cell histiocytosis cells, with secondary interlobular fibrosis, ductal dilatation, and exocrine gland atrophy. The structural damage to the pancreas represents a chronic process with fibrosis being the major feature. It is well recognised that the cellularity of lesions affected by Langerhans' cell histiocytosis decreases with time, older lesions tend to contain fewer Langerhans' cell histiocytosis cells. In spontaneously resolved lesions, the

pathology is dominated by fibrosis and increasing number of macrophages.[10] The fibroblastic activity may be a response to local cytokine production, either derived from the Langerhans' cell histiocytosis cells or other inflammatory cells. The functional damage to certain vital organs such as the lungs, liver and pancreas may result from changes secondary to fibrosis rather than being caused directly by the cellular infiltrate.

In summary, we report the case of an infant with fatal multisystem Langerhans' cell histiocytosis in which the pancreas and bowel were involved. Pancreatic involvement should be considered in patients with extensive disease, especially in cases where the upper gatrointestinal tract is involved. The histological changes of the pancreas resemble those of chronic pancreatitis with Langerhans' cell histiocytosis cells as part of the cellular infiltrate. Improved imaging techniques such as nuclear magnetic resonance scanning may facilitate earlier diagnosis of pancreatic involvement

1 Writing Group of the Histiocyte Society. Histiocytosis syndromes in children. *Lancet* 1987; i: 208–9.
2 Beckstead JH, Wood GS, Turner RR. Histiocytosis cells and Langerhans' cells: enzyme histochemical and immunologic similarities. *Hum Pathol* 1984; **15**: 826–33.
3 Groh V, Gadner H, Radaszkiewicz T, Rappersberger K, Konard K, Wolff K, Stingl G. The phenotypic spectrum of histiocytosis X cells. *J Invest Dermatol* 1988; **90**: 441–7.
4 Lucaya J. Histiocytosis X. *Am J Dis Child* 1971; **121**: 289–95.
5 Lahey ME. Histiocytosis X – an analysis of prognostic factors. *J Pediatr* 1975; **87**: 184–9.
6 Hyams JS, Haswell JE, Gerber MA, Berman MM. Colonic ulceration in histiocytosis X. *J Pediatr Gastroenterol Nutr* 1985; **4**: 286–90.
7 Egeler RM, Schipper MEI, Heymans HSA. Gastrointestinal involvement in Langerhans' cell histiocytosis (histiocytosis X): a clinical report of three cases. *Eur J Pediatr* 1990; **149**: 325–9.
8 Idibi O, Hamoudi AB. Primary histiocytosis X of bowel. *Pediatr Pathol* 1984; **2**: 492.
9 Keeling JW, Harris JT. Intestinal malabsorption in infants with histiocytosis X. *Arch Dis Child* 1973; **48**: 350–4.
10 Malone M. The histiocytoses of childhood. *Histopathology* 1991; **19**: 105–9.